REMARKS

Claims 24-32 were pending in the application. Claim 24 has been amended. Accordingly, after the amendments presented herein have been entered, claims 24-32 will remain pending. For the Examiner's convenience all of the pending claims are set forth herein in Appendix A.

Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of the following: (a) The previous rejection of claims 24-32 and 47 as not being patentably distinct from claims 6, 7, and 15-17 of commonly assigned application serial no. 09/519,019; (b) The previous provisional rejection of claims 24-32 and 47 under 35 U.S.C. § 103(a) as being obvious over copending Application No. 09/519, 019 in view of the WO Patent Application 98/08868, Kroin et al (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980; and (c) The previous rejection of claims 24, 31, and 47 under 35 U.S.C. § 102(b) as being anticipated by the WO Patent Application 98/08868 in view of the WO Patent Application 95/20980.

The previous rejection of claim 25 under 35 U.S.C. § 112, second paragraph; the previous rejection of claims 24, 28, 30, 31 and 47 under 35 U.S.C. § 102(a) as being anticipated by the WO Patent Application 99/10374; and the previous rejection of claims 24, 28, 30, 31 and 47 under 35 U.S.C. § 102(a) as being anticipated by the WO Patent Application 99/10374 in view of WO Patent Application 95/20980 are not mentioned in the present Office action. Accordingly, Applicants assume that these rejections have also been overcome and respectfully request that the Examiner so indicate.

Objections to the Claims

The Examiner has objected to claim 24 because, according to the Examiner, "[a]t claim 24, line 4, 'polypeptide' should be changed to 'peptide' so that the claim terminology is consistent."

Without acquiescing to the validity of the Examiner's objection, Applicants have amended claim 24, thereby rendering the foregoing objection moot. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this objection to claim 24.

Provisional Rejection of Claims 24-32 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 24-32 under the judicially created doctrine of obviousness-type double patenting as, "being unpatentable over claims 6, 7, and 15-17 of copending Application No. 09/519,019 in view of WO Patent Application 98/08868, Kroin et al. (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980."

Applicants respectfully submit that when the pending claims in the present application are indicated as allowable, Applicants will consider submitting, if appropriate, a terminal disclaimer complying with 37 C.F.R. §1.321 (b) and (c) which will obviate this rejection. The filing of this terminal disclaimer should in no way be construed as an acquiescence to the Examiner's obviousness-type double patenting rejection and will be done solely to expedite the prosecution of the application.

Rejection of Claims 24, 25, 31, and 32 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 24, 25, 31, 32, and 47 under 35 U.S.C. § 102(b) as, "being anticipated by the WO Patent Application 98/08868 in view of the Applicants' admission at page 11, lines 2-3 of the specification." In particular, the Examiner is of the opinion that

> [t]he WO Patent Application '868 teaches β-amyloid peptide derivatives which are administered in vivo to the CNS or across the BBB for the diagnosis and treatment of amyloidogenic diseases. Administration can be as a single bolus or several divided doses. Supplementary active compound can be incorporated into the compositions. Two or more of the β-amyloid peptide derivatives may be used in combination. Particularly exemplified β-amyloid peptide derivatives may be used in combination. Particularly exemplified β-amyloid peptide derivatives include PPI-558, PPI-578, PPI-655, and P[P]I-657. .... With respect to the teachings in the WO Patent Application '868 of the administration of a single β-

amyloid peptide derivatives, Applicants admit at page 11, lines 2-3, that the β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, the teachings of the WO Patent Application '868 of the administration of a single β-amyloid peptide derivative constitute an inherent teaching of the administration of both a β-amyloid peptide derivative and a P-glycoprotein inhibitor. Note that the claims do not contain any limitations requiring the β-amyloid peptide derivatives and the P-glycoprotein inhibitors to be chemically distinct compounds. It follows then that the WO Patent Application '868's teaching of administering the β-amyloid peptide derivatives either as a single bolus or in several divided doses constitutes an inherent teaching of the simultaneous or non-simultaneous administration of a β-amyloid peptide derivative and a P-glycoprotein inhibitor. With respect to the teachings of the WO Patent Application '868 of the administration of two or more β-amyloid peptide derivatives in combination, again Applicants admit at page 11, lines 2-3, that β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, at least on of the β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as corresponding to Applicants' β-amyloid peptide derivative, and at least one of the other β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as inherently corresponding to Applicants' P-glycoprotein inhibitor.

Applicants respectfully traverse the foregoing rejection for the following reasons. As amended, claim 24 and claims depending therefrom are directed to methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, ***wherein the P-glycoprotein inhibitor is not a β-amyloid peptide derivative,*** a liposome or Tween-80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

For a prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that the '868 application fails to teach or suggest methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which ***the P-glycoprotein inhibitor is not a β-amyloid peptide derivative***. Accordingly, the '868 application does not anticipate the pending claims and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 24, 25, and 27-32 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 24, 25, and 27-32 under 35 U.S.C. § 103(a) as being, "obvious over the WO Patent Application 98/08868 as applied against claims 24, 25, 31 and 32 above, and further in view of Kroin et al. (U.S. Patent No. 5,776,939) or the WO Patent Application 95/20908."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, since the proposed reference fails to provide the necessary motivation and a reasonable expectation of success for the ordinarily skilled artisan to arrive at Applicant's invention. As indicated above, the '868 application fails to teach or suggest methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which ***the P-glycoprotein inhibitor is not a β-amyloid peptide derivative***. The Examiner relies on

M.P.E.P. § 2123 to support his argument that "the disclosure of a reference is not limited to the reference's most preferred embodiments, and that the preferred embodiment of a reference does not teach away from the reference's ***disclosed*** non-preferred embodiments." ***Emphasis added.*** The case cited in M.P.E.P. § 2123 relates to an invention directed to an epoxy impregnated fiber-reinforced printed circuit material. The applied prior art reference

> taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, ***disclosed that epoxy was known for this use,*** but that epoxy impregnated circuit boards have "relatively acceptable dimensional stability " and "some degree of flexibility,"but are inferior to circuit boards impregnated with polyester -imide resins.The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since "Gurley asserted no discovery beyond what was known in the art."27 F.3d at 554,31 USPQ2d at 1132.). ***Emphasis added.***

In the present case, the '868 application ***does not disclose*** or suggest methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which ***the P-glycoprotein inhibitor is not a β-amyloid peptide derivative.***

Moreover, the secondary references of Kroin *et al.* (U.S. Patent No. 5,776,939) and the WO Patent Application 95/20908 do not make up for the above-stated deficiencies of the '868 application.

In summary, it is Applicant's position that the references relied upon by the Examiner, alone or in combination, fail to teach or suggest the claimed invention. For the foregoing reasons, this section 103(a) rejection is believed to be improper and Applicants respectfully request that it be reconsidered and withdrawn as applied to the currently pending claims.

SUMMARY

Reconsideration and allowance of all the pending claims is respectfully requested.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

Maria Laccotripe Zacharakis, Ph.D.
Limited Recognition Under 37 CFR §10.9(b)
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: October 3, 2003

Appendix A

24. **(Currently Amended)** A method for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, wherein said P-glycoprotein inhibitor is not a β-amyloid peptide derivative, liposome or Tween-80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

25. **(Previously Presented)** The method of claim 24, wherein the β-amyloid peptide derivative is selected from the group consisting of PPI-558, PPI-657, PPI-1019, PPI-578, and PPI-655.

26. **(Original)**The method of claim 25, wherein the β-amyloid peptide derivative is PPI-1019.

27. **(Original)**The method of claim 24, wherein the P-glycoprotein inhibitor is valspodar.

28. **(Original)**The method of claim 24, wherein the P-glycoprotein inhibitor is cyclosporin A.

29. **(Original)** The method of claim 24, wherein the P-glycoprotein inhibitor is selected from the group consisting of antiarrhythmics, antibiotics, antifungals, calcium channel blockers, cancer chemotherapeutics, hormones, antiparasites, local anesthetics, phenothiazines, and tricyclic antidepressants.

30. **(Original)** The method of claim 24, further comprising administering to the subject a cytochrome P450 inhibitor.

31. **(Original)** The method of claim 24, wherein the β-amyloid peptide derivative and the P-glycoprotein inhibitor are administered simultaneously.

32. **(Original)** The method of claim 24, wherein the β-amyloid peptide derivative and the P-glycoprotein inhibitor are administered at different times.